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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,890	01/29/2002	Timothy A. Coleman	PF537	3639

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 11/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,890	COLEMAN ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover she t with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,17,18 and 22-25* is/are pending in the application.

4a) Of the above claim(s) *10 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,17 and 22-24* is/are rejected.

7)☒ Claim(s) *9 and 25* is/are objected to.

8)☒ Claim(s) *1-10,17,18 and 22-25* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 January 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1, 3-5, and 17) drawn to scaffolded fusion polypeptides in Response filed 12 September 2003 is acknowledged. The traversal is on the ground(s) that: (a) no successful showing of a "serious burden" pursuant to MPEP §803 in the Restriction Requirement, (b) polynucleotides and polypeptides often published together therefore no search burden, (c) methods of screening molecules that bind polypeptides often published together.

2. This is not found persuasive because the Examiner set forth the search and examination burdens in the Restricition Requirement mailed 12 August 2003. The polypeptide and polynucleotide are not necessarily linked as one can be made and used without the other as set forth in the previous Office Action (12 August 2003). On the grounds of publication of polynucleotides, polypeptides, and screening methods, it represents the opinion of the Applicant with no cited evidence that the polynucleotides, polypeptides, and methods of screening present in the instant Application. Therefore, it can only be established by conducting the search and examination of these groups.

3. Applicant further requests rejoinder of Groups I-III and/or Groups I and V. First it must be noted that newly submitted claims **22-25** are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: SEQ ID NO's 8, 15, 16, and 31 were not originally presented and have been added after the restriction requirement. Further, currently amended claims **5** and **9** are directed to an invention that is independent or

distinct from the invention originally claimed for the following reasons: SEQ ID NO's 5, 6, and 7 were not originally presented and have been added after the restriction requirement.

4. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims **5** and **9 (each in part) and 22-25** may withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. However, in the interest of providing Applicant with a full and complete Office Action on the claimed subject matter, the Examiner has included SEQ ID NO's 3, 4, 5, 6, 7, 8, 10, 15, 16, and 31 thereby rejoining Groups I, II, and III. The instant Office Action will search and examine claims 1-9 and 22-25. The Examiner further notes that upon reaching allowable subject matter, claims 10 and 18 (drawn to a nucleic acid encoding the scaffolded protein and a method of screening molecules that bind said scaffolded fusion polypeptide) as currently presented will be considered for rejoinder. Yet, the requirement is still deemed proper for purposes of beginning examination is made FINAL.

Drawings

6. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: numbers. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

7. Claims **9** and **25** are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims **1-8 and 22-24** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a scaffolded fusion polypeptide comprising SEQ ID NO: 10 and SEQ ID NO: 31*, does not reasonably provide enablement for *any other scaffolded fusion polypeptide*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

9. The claims are drawn very broadly to a scaffolded fusion polypeptide comprising one or more modules, each module comprising a functional polypeptide domain fused to a scaffold domain. The language of said claims encompasses a massive genus of functional domains flanked by scaffolds with no explicit delineation of the fusion polypeptide itself.

10. The specification teaches that SEQ ID NO: 10 is a CCR5 scaffolded fusion polypeptide and SEQ ID NO: 31 is a CCR5 scaffolded fusion polypeptide with a signal sequence.

11. The specification fails to provide any guidance for the successful construction and/or expression of other scaffolded fusion polypeptides, and since resolution of the various complications in regards to protein biochemistry, especially with transmembrane proteins, is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations a wide range of transmembrane proteins, identification of their functional domains, cloning, and then construction with the flanking scaffolds. This would then be followed by expression and characterization of each and every clone to insure that the scaffolded fusion polypeptide so constructed would have the desired activity. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed, as it constitutes an invitation to experiment (see MPEP §2164.06).

12. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptide sequences to form fusion polypeptides based solely on its performance of two examples of CCR5 fusion polypeptides highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of making the claimed scaffolded fusion polypeptides, such a disclosure would not be considered enabling since the state protein biochemistry, especially transmembrane proteins, is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

13. The following references are cited herein to illustrate the state of the art of protein biochemistry.

14. On the breadth of the claims, metal chelating motifs, specifically zinc binding motifs (e.g. "zinc fingers"), US 6,007,988 (28 December 1999) Choo *et al.* and US Re. 35,585 (12 August 1997) Fernandez-Pol teach that zinc finger binding motif is an α-helical structure found in proteins which binds Zn^{2+}. These motifs while known in the art are numerous and vary in their ability to bind Zn^{2+} (Col. 3-5). From the claims as written it is unclear as to which zinc finger is required to practice the invention thus requiring trial and error to find the zinc finger motifs which work in the invention as claimed.

15. On the nature of the invention, Howard *et al.* (March 2001) "Orphan G-protein-coupled receptors and natural ligand discovery." TRENDS in Pharmocological Sciences 22(3): 132-140 naturally occurring receptors, specifically G-protein coupled receptors (e.g. "GPCRs"), are a massive diverse genus of receptors responsible for the transduction of a diverse array of extracellular signals, including but not limited to light, Ca^{2+}, odorants, amino acids, nucleotides, peptides, fatty acid derivatives, and polypeptide ligands (pp. 132). Howard *et al.* teaches that GPCRs are both structurally and functionally diverse (pp. 132-133). Thus the skilled artisan is

confronted with a massive genus of receptors, and even when limited only to seven-transmembrane-domain receptors, it still remains at over 1000 family members, presenting an overwhelming burden of experimentation to practice the full-extent of the claims.

16. Raport *et al.* (19 July 1996) "Molecular Cloning and Functional Characterization of a Novel Human CC Chemokine Receptor (CCR5) for RANTES, MIP-1β, and MIP-1α." The Journal of Biological Chemistry **271**(29): 17161-17166. Raport *et al.* teaches a CCR5 (a G-protein coupled receptor) thus meeting the limitations of claims 1-2 (Figure 1). Raport *et al.* teaches a CCR5 that contains **SEQ ID NO: 5** thus comprising a single zinc chelating which is connected to the rest of the protein by a stretch of amino acids (Figure 5). However, Raport *et al.* does not teach that the inclusion of SEQ ID NO: 5 has made the CCR5 soluble (pp. 17161). Therefore the art teaches that a CCR5 can contain a zinc-chelating motif but not be soluble.

17. On the prior art, Ling *et al.* (July 1999) "Five-transmembrane domains appear sufficient for a G protein-coupled receptor: Functional five-transmembrane domain chemokine receptors." PNAS **96**: 7922-7927 teaches that five transmembrane domains are required for CCR5 to function (Figures 3-5) thus the claims as written may not be fulfilled unless the chosen GPCR has a minimum number of transmembrane-domains. Thus the skilled artisan is confronted with undue experimentation to determine what the minimum number of transmembrane domains are required for each of the over 1000 GPCRs.

18. On the question of using the instant invention, Harrison *et al.* (April 1999) "Copper chaperones: function, structure and copper-binding properties." J Biol Inorg Chem. **4**(2): 145-153 teach the conserved "MXCXXC" metal-binding motif (p. 145). However, it remains unclear

as to how the skilled artisan would use a scaffolded fusion protein containing a metal-biding motif.

19. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from two examples of successful construction of scaffolded fusion polypeptides to the making of other non-specified scaffolded fusion polypeptides as exemplified in the references herein.

20. Claims **1-8, 17,** and **22-24** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

21. The claims are drawn to polypeptides having a "functional polypeptide" fused to a "scaffold domain". The claims do not require that the "functional polypeptide" to possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of polypeptides that is defined by possessing a general, non-disclosed biological function of some variety.

22. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is the recitation of an as of yet undisclosed function and/or

activity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 10 and SEQ ID NO: 31. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus [MPEP §2163 ¶3a(ii)]. For instance, Rhoads & Friedberg (April 1997) "Sequence motifs for calmodulin recognition." FASEB J. **11**(5): 331-340 teach the great variety of Ca^{2+} binding motifs. Further, Laity *et al.* (February 2001) "Zinc finger proteins: new insights into structural and functional diversity." Current Opinion in Structural Biology **11**(1): 39-46 teach that zinc binding domains exhibit great structural and functional diversity (pp. 39) thus requiring a greater, more detailed disclosure in the instant Specification to support the written description requirement.

23. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

24. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

25. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 10 and SEQ ID NO: 31, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Summary

26. Claims **1-8, 17,** and **22-24** are hereby rejected.

27. Claims **9** and **25** are free of the prior art.

28. The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

a. US 5,861,495 (19 January 1999) Hillman *et al.*

b. US 5,905,146 (18 May 1999) Lecka-Czernik

c. US 6,534,261 B1 (18 March 2003) Cox, III *et al.*

d. US 6,010,877 (4 January 2000) Sathe *et al.*

e. US 5,789,538 (4 August 1998) Rebar & Pabo

f. US 5,981,223 (9 November 1999) Sathe *et al.*

g. US 6,007,988 (28 December 1999) Choo *et al.*

h. US 5,821,067 (13 October 1998) Grandy *et al.*

i. US Re. 35,585 (12 August 1997) Fernandez-Pol

j. US 5,948,890 (7 September 1999) Soppet *et al.*

k. US 5,837,809 (17 November 1998) Grandy *et al.*

l. US 5,763,183 (9 June 1998) Pesonen *et al.* US

m. US Patent Application Publication US 2002/0137891 A1 (26 September 2002) Hill *et al.*

n. Loomans *et al.* (March 1998) "Histidine-based zinc-binding sequences and the antimicrobial activity of calprotectin." J Infect Dis. **177**(3): 812-814

o. MacKenzie *et al.* (August 1995) "Bifunctional fusion proteins consisting of a single-chain antibody and an engineered lanthanide-binding protein." Immunotechnology **1**(2): 139-150

p. Eng *et al.* (1 November 1998) "Sequence Analyses and Phylogentic Characterization of the ZIP Family of Metal Ion Transport Proteins." J. Membrane Biol. **166**(1): 1-7

q. Lewit-Bentley & Réty (December 2000) "EF-hand calcium-binding proteins." Current Opinion in Structural Biology **10**(6): 637-643

r. Hooper (31 October 1994) "Families of zinc metalloproteases." FEBS Lett. **354**(1): 1-6

s. MacLennan *et al.* (August 1998) "Structure-function Relationships in the Ca^{2+}-Binding and Translocation Domain of SERCA1: physiological correlates in Brody disease." Acta Physiol. Scand. **163**: 55-67

t. Procyshyn & Reid (21 January 1994) "A Structure/Activity Study of Calcium Affinity and Selectivity Using a Synthetic Peptide Model of the Helix-Loop-Helix Calcium-binding Motif." The Journal of Biological Chemistry **269**(3): 1641-1647

u. Choe *et al.* (28 June 1996) "The β-Chemokine Receptors CCR3 and CCR5 Facilitate Infection by Primary HIV-1 Isolates." Cell **85**: 1135-1148

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
November 14, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER